REMARKS

Upon entry of this amendment, claims 1-4 and 19-24 are in front of the Examiner. Claims 5-17 were withdrawn from examination as being directed to non-elected subject matter after a restriction requirement. Claim 18 was canceled without prejudice. New claims 22-26 were added. Support for Applicants' amendments and the newly added claims is found throughout the specification. No new matter has been entered.

Election/Restriction

The Examiner has acknowledged Applicants' election, with traverse, of Group I (claims 1-4 and 18-21) in the Response filed on June 27, 2005.

Specification and Drawing

As suggested by the Examiner, Applicants request the title to be amended as indicated above. In addition, the specification is amended to update the status of the parent application as abandoned. Further, the specification is amended to correctly describe the previously submitted drawings. No changes were made to the drawings, and no new matter was introduced to the specification, as the drawings were clearly marked and the amended specification simply recites what was already described in the drawings. Reconsideration and withdrawal of the objections to the specification are requested.

Claim objections

Claims 1-4 were objected to as encompassing non-elected inventions. Applicants amended the claims without prejudice so that the non-elected inventions no longer are recited. Applicants reserve the right to pursue the deleted subject matter in a later divisional or continuation application.

Claims 1, 2, and 18-21 were objected to as reciting an abbreviation. Applicants respectfully traverse. The term "ptc therapeutic" is a defined term, clearly described in the specification at page 12, lines 17-22. Accordingly Applicants respectfully request this ground of objection be withdrawn.

Rejection under 35 U.S.C. §112 first paragraph, enablement

Claims 1-4 and 18-21 were rejected as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

To expedite prosecution, Applicants have amended the claims to more particularly point out the claimed subject matter. Such amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Regarding claims 1, 3, and 4, the specification provides support for methods of inhibiting the growth and proliferation of transformed cells. *See*, for example, page 15, line 7-page 16, line 4.

> . . . In general, the method can be characterized as including a step of administering to an animal an amount of a ptc. . . therapeutic effective to alter the growth state of a treated lung tissue. The mode of administration and dosage regimens will vary depending on the phenotype of, and desired effect on the target lung tissue. . . . (page 15, lines 8-10)
>
> In one aspect, the present invention provides pharmaceutical preparations and methods for controlling the proliferation of lung tissue utilizing, as an active ingredient, a hedgehog polypeptide or a mimetic thereof. The invention also relates to methods of controlling proliferation of mesenchymal and epithelial cells of the tissue by use of the pharmaceutical preparations of the invention. (page 15, lines 15-19)
>
> The formulations of the present invention may be used as part of regimens in the treatment of disorders of, surgical repair of, or transplantation of lung tissues and whole organs. The methods and compositions disclosed herein also provide for the treatment of a variety of proliferative cancerous disorders effecting lung tissue. . . . (page 15, lines 20-25)
>
> In certain embodiments, the subject compositions can be used to inhibit, rather than promote, growth of lung-derived tissue. For instance, certain of the compositions disclosed herein may be applied to the treatment or prevention of a variety hyperplastic or neoplastic conditions. The method can find application for the treatment or prophylaxis of, e.g., used to inhibit the growth and metastasis of lung cancer cells. For instance, inhibitory forms of the the subject ptc, hedgehog and fgf-10 therapeutics may be used as part of a treatment program for small cell lung cancer (SCLC), as well as non-small cell lung cancer (NSCLC), such as adenocarcinoma, lung cell carcinoma and squamus cell carcinoma. (page 15, line 26-page 16, line 4)

In addition to hedgehog mutants that lost the wildtype's proliferation-promoting activities, the application describes the characteristics of useful ptc therapeutics and how to identify such therapeutics (*See*, section V beginning on page 48). Furthermore, the experimental results provide the phenotypes of hedgehog null mice, thus indicating the effects of the lack of active hedgehog. Similar effects, i.e. the lack of or attenuation of active hedgehog in an animal, can be achieved by administering to the animal or overexpressing in the animal a hedgehog mutant with little or no wildtype activity, or a ptc therapeutic that inhibits the hedgehog/patched pathway. Either approach would negatively regulate hedgehog signal transduction. The hedgehog null mice results, therefore, are representative of the kind of results one would reasonably expect when using a hedgehog mutant lacking activity or a ptc therapeutic that antagonizes hedgehog/ptc signal transduction. The making and testing of a range of ptc therapeutics can be done without undue experimentation.

Turning to claim 2, the specification also provides ample support for the promotion of normal lung tissue's growth and maintenance. In addition to hedgehog protein and its proliferative derivatives, small molecules and antisense constructs to inhibit patched's inhibitory activities are described. See, for example, page 12, lines 17-22; page 57, line 3-page 60, line 3; page 60, line 26-page 62, line 8.

In these paragraphs, antagonists of patched proteins which would attenuate the inhibitory effect of patched, thereby potentiating hedgehog-mediated cell proliferation and differentiation are described. These agent, defined as "proliferative" forms of ptc therapeutics, can be therapeutically useful to promote growth and repair of normal tissue after damages from various disease conditions or transplantation, as described in the specification.

Applicants contend that the amended claims are enabled throughout their scope. The specification provides ample support for methods of inhibiting proliferation and growth of lung cancer cells using ptc therapeutics that inhibit hedgehog/patched signal transduction (e.g., hedgehog antagonists). The specification further supports methods for promoting growth or formation of normal lung tissue using ptc therapeutics that promote hedgehog/patched signal transduction (e.g., hedgehog agonists). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112 first paragraph, written description

Claims 1-4 and 18-21 were rejected for allegedly failing to comply with written description requirement. Applicants respectfully traverse. Contrary to the Examiner's assertion, as indicated in the above section, the specification contains ample examples other than sonic hedgehog protein that can be used to practice the claimed methods. See, for example, page 12, lines 17-22; page 57, line 3-page 60, line 3; page 60, line 26-page 62, line 8. The compositions to be used in the claimed methods are described, and the administration of the composition is described in section IV. Accordingly, this rejection appears to be unfounded in fact and should be withdrawn.

Rejection under 35 U.S.C. §112 second paragraph

Claim 19 was rejected as indefinite by the Examiner, who alleges the term "small" is a relative term and renders the term "organic molecule" indefinite. Applicants respectfully disagree. Applicants submit the term "small organic molecule" is a term of art whose meaning was understood by those skilled in the art. A review of the literature prior to the priority date reveals that it was well accepted that small molecules are organic molecules with a molecular weight of less than about 1000 daltons. The term is used to differentiate these organic molecules from typical large biomolecules like nucleic acids, proteins, and complex carbohydrates like heparin and starch. In support of this understanding, Applicants respectfully direct the Examiner's attention to the following exemplary citations:

(1) Free Radical Toxicology (Target Organ Toxicology Series) by Kendall B. Wallace, Publisher: Taylor & Francis; (June 1997), ISBN: 1560326328, which states on page 148 "... is associated with three chemically distinct types of oxidants formed by iron-mediated Fenton reactions in the presence of DNA. Small-Molecule Antioxidants - Numerous **small molecules (<1000 MW)** with high reactivity toward oxidants have been described. Three of these, vitamin E, ascorbic acid, and glutathione, play essential ..." [emphasis added]

(2) Molecular Methods for Virus Detection by Danny Wiedbrauk and Daniel Farkas, Publisher: Academic Press, 1st edition (January 15, 1995), ISBN: 0127489207, which states on page 154 "Electrochemiluminescent labels are

relatively **small molecules (--1000 dalton)** that are extremely stable and may be coupled to nucleic acids, haptens, or proteins without affecting immunoreactivity or ..." [emphasis added]

(3) Neurotoxicology: In Vitro by V. W. Pentreath (Editor), Publisher: Taylor & Francis; 1 edition (June 1, 1999), ISBN: 0748403884, which states on page 200 "... Modalities of intercellular communication. Hormones (V) and growth factors (0) are transported to the targets via blood. Ions and **small molecules (< 1000 Da)** can pass through gap junctions from one cell to its neighbours and influence the function of the connecting cells. ..." [emphasis added]

(4) New Frontiers in Cancer Causation: Proceedings of the Second International Conference on Theories of Carcinogenesis, by Olav Hilmar Iversen (Editor), Publisher: Taylor & Francis, (September 1993), ISBN: 1560322519, which states on page 186 "... (connexons). Each cell contributes a hemichannel composed of a hexamer of proteins (connexins). Clusters of these connexons allow ions and **small molecules (below 1000 daltons)** to freely equilibrate between coupled cells. There exists a family of highly conserved genes coding for these proteins ..." [emphasis added]

(5) Dermatotoxicology by Francis Nicholas Marzulli (Editor), Howard I. Maibach (Editor), Publisher: Taylor & Francis; 5th edition (February 1996), ISBN: 1560323566, which states on Page 147 "... with skin proteins to form complete antigens and how these structures are recognized by T-cell receptors. SOME CHEMICAL REMINDERS Haptens (**small molecules with a molecular mass less than 1000 Da**) interact with biological macromolecules by mechanisms leading to the formation of bonds of various strengths between the two entities. ..." [emphasis added]

Copies of these articles are provided as **Exhibit A**. In addition, Applicants provide herewith a copy of a PubMed printout for a search of the term "small molecule". An exemplary page of twenty results roughly contemporaneous with the filing of the priority document is provided as **Exhibit B**, together with the abstracts of the last ten of these articles. All of these references use the

term consistently with the above references, i.e., to refer to low molecular weight organic compounds, and the particular small molecules singled out by these references are all consistent with the understanding set forth above. Moreover, these articles use the term in the abstract and/or title – where it is critical that the matter being described be clear, simple and well understood. It would be unfathomable to use a term in the title or abstract that would invite confusion or misunderstanding among those of ordinary skill in the art. And hundreds of references, as can readily be seen, used the term "small molecule" in a similar manner well before the filing of the present application. Accordingly, Applicants submit that the citations taken together are indicative of the well accepted meaning of small molecules or small organic compounds, and that the meaning of such terms would be understood by one skilled in the art. *In re Hammack*, 166 USPQ 204, 208 (C.C.P.A 1970).

Rejection under 35 U.S.C. §102(a)

Claims 1-4 and 18-22 were rejected as allegedly being anticipated by Fujita et al., BBRC 238: 658-655. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978). "The identical invention must be shown in as complete detail as is contained in the claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Applicants contend that Fujita et al. fail to anticipate the claimed invention. Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out the claimed subject matter. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

As amended, claims 1, 3, and 4 recite that the applicable ptc therapeutic is a small organic molecule that inhibits or reduces cell proliferation or growth. There is no description or teaching in

Fujita et al. of inhibiting cancer cell proliferation or growth using a small organic molecule. Accordingly, Fujita et al. fail to satisfy the criteria necessary for anticipating the claimed subject matter.

As amended, claim 2, and new claims 22-24 which are dependent on claim 2, recite methods of administering ptc therapeutics to normal lung tissue. Fujita et al. describes the proliferative effect of N-terminal fragment of Sonic hedgehog on carcinoma and other cancer cells. Although non-cancerous cells are discussed in the comparison (and shown *not* to have significant levels of Shh expression), Fujita et al. is silent with regard to the effect of the Sonic hedgehog fragment on normal lung tissue. Fujita et al. quotes from another reference that overexpression of Shh has a proliferative effect on lung mesenchymal cells in vivo but no results or facts are presented to provide the support necessary to anticipate the presently claimed invention. Accordingly, Fujita et al. fail to satisfy the criteria for anticipating the claimed subject matter.

In light of Applicants' arguments and amendments, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the above amendments and arguments, Applicant believes the pending application is in condition for allowance. Applicant believes no fee is due with this response other than the fees indicated on the accompanying fee transmittal. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. HUIP-P02-032 from which the undersigned is authorized to draw.

Dated: January 20, 2006

Respectfully submitted,

By_____

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